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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/633,697	08/07/2000	Gerard Andrew Potter	A33403PCT USA-A	3756

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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	20

DATE MAILED: 08/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/633,697	POTTER ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-57* is/are pending in the application.

4a) Of the above claim(s) *53-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-42,44,47,49-52 and 57* is/are rejected.

7)☒ Claim(s) *43,45,46 and 48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 6/20/02. Applicants have amended claims 37, 42, 45, 48, and 52. Claim 57 is new. There are twenty-one claims pending and seventeen under consideration. Claims 37-49 and 57 are compound claims. Claim 50 is a composition claim. Claim 51 is a method of preparation claim. Claim 52 is a use claim. The application concerns some benzyl and cinnamyl carbamate prodrugs. This is the second action on the merits. This action is made non-Final because new written description, enablement, and indefiniteness rejections are being made.

Response to Amendment

2. Applicants' amendments to the claims limiting the scope overcomes the improper Markush rejection made in point #3 of the previous office action. Applicants new abstract overcomes the objection made in point #4. Applicants' amendments replacing "thiol" by "mercapto" overcomes the indefiniteness rejection made in point #6. Applicants' deletion of "phenanthyl" from claim 42 overcomes the indefiniteness rejection made in point #8. Applicants deletion of X = hydrogen as a possible variable overcomes all the anticipation rejections made in points #11-#15.

Election/Restrictions

3. Claims 53-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 37-42, 44, and 49-52 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The structural element in formula (Z) "drug" is indefinite. Names, structures, and chemical formulas precisely define organic molecules. Attempting to define structure by function is not proper when the structures can be clearly expressed in terms that are more precise. It is not sufficient to define a chemical structure solely by its principal biological property. The Examiner suggests using the drug elements from the structures in claims 45 and 46, since that is what was searched.

Applicants make three arguments. Firstly, that the word "drug" is defined in the dictionary and its meaning readily understood as a substance used in medicine to affect a treatment. Secondly, that the Examiner in making the art rejections in

the previous action understood, at least some of its meaning. Thirdly, that such language was been allowed previously in US Patents.

This is not persuasive. Applicants provide guidance in four portions of the specification as to their intended meaning. These are in paragraph 2, page 1, the paragraph spanning pages 4 to 5, in the second and third paragraph on page 5. Lastly, in the structural formulas X-XIII, XIV-XVII, and XXIII-XXXII wherein "drug" is the radical attached to the right side of the -O-C(O)- group in each formula. The last five lines of claim 37 mean that the molecule "drug" must possess an NH_2, NHR, OH, SH, or CO_2H functional group.

The issue is not the meaning of the word "drug", which the Examiner admits is well understood but rather the chemical structures intended when "drug" is incorporated as a univalent radical in a chemical formula. The skilled organic chemist would readily understand what is intended by all the formulas listed above but Applicants obviously intend a broader meaning. The other portions of the specification cited above do not make clear what additional structures are intended. They use open language "for example", "may be", "any desired effect", and "include". They refer to biological effects and mechanisms of action, not the structural features required by the organic chemist to understand Applicants intended meaning. Are the antifolate "drugs" restricted to antifolates listed in the

US Pharmacopoeia or are all molecules that inhibit folate synthesis covered? Does alkylating agent mean the nitrogen mustards presently used clinically for cancer treatment or are all alkyl iodides, triflates, mesylates, and bromides containing a NH_2, NHR, OH, SH, or CO_2H functional group intended?

The Examiner used the formulas referred to above to make the art rejections over molecules containing "drug" radicals. The issue is what else is intended. Finally, the indefiniteness remains despite what was allowed in another case. The U.S. Court of Customs and Patent Appeals wrote *In re Giolito* 188 USPQ 645: "We reject appellants' argument that the instant claims are allowable because similar claims have been allowed in a patent. It is immaterial whether similar claims have been allowed to others. See *In re Margaroli,* 50 CCPA 1400, 318 F.2d 348, 138 USPQ 158 (1963); *In re Wright*, 45 CCPA 1005, 256 F.2d 583, 118 USPQ 287 (1958); *In re Launder*, 41 CCPA 887, 212 F.2d 603, 101 USPQ 391 (1954)".

5. Claims 38-41, 44, and 49-52 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitations in claims 38-41 "wherein hydroxylation ... the drug moiety" is unduly functional. The limitation in claim 49 is also unduly functional. Names, structures, and

chemical formulas precisely define organic molecules. Attempting to define structure by function is not proper when the structures can be clearly expressed in terms that are more precise. It is not sufficient to define a chemical structure solely by a biological property.

Applicants argue that this is not a functional limitation and that the specification defines what is meant to the skilled organic chemist. This is not persuasive. Enzymatic hydroxylation is described in lines 10-15, page 3, lines 22-25, page 2, the fourth complete paragraph in page 3, the penultimate paragraph on page 4, lines 13-14, page 5, and the paragraph spanning pages 5 to 6. Presumably, claim 38 further limits claim 37. That is, there are compounds included in formula (Z) which do not release the drug moiety when hydroxlyated on the aromatic ring. The passages cited provide no guidance as to which structures have this ability and which do not. If separating compounds into two classes based on their metabolic fate is not a functional limitation, what is it?

6. Claims 37-42, 44, and 49-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367,

73 USPQ 482 (CCPA 1947). The term "drug" in claim 37 is used by the claim to mean "drug or diagnostic agent," while the accepted meaning is "drug." Applicants cite a dictionary meaning of the word drug which is incompatible with the additional meaning expressed in lines 2-7, page 5 of the specification.

7. Claim 57 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Formula (XXXII) lacks a double bond in the carbamate functional group.

8. Claims 37-42, 44, and 49-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Claim 37 requires the compounds of formula (Z) to be a "prodrug". Determining if any particular substance fitting formula (Z) is a prodrug will involve extensive experimentation. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically

active. Determining whether a particular compound meets these three criteria in a clinical trial setting passes the threshold of undue experimentation.

Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the collaborative team that must be employed to make a prodrug. The targeted prodrugs mentioned to in the last line of the reference include the self-targeting anti-tumor drugs referred to on page 5 of the specification. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. Finally, concerning the amine containing drugs, compounds where A = NH or NR, Shan (J. Pharmaceutical Sci.) indicates in the first paragraph, page 765 that "[a]pplying similar strategies to the preparation of prodrugs of amine-containing drugs is somewhat more problematic ...". Thus indicating that the research program outlined above may be inconclusive when applied to drugs with A = nitrogen..

9. Claims 37-42, 44, and 49-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While functional language is permitted in chemical claims the word "drug" as a chemical radical is unduly functional and does not convey possession of the invention. The MPEP states in §2162 I.A. that "[t]he claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." As explained above use of the word "drug" as a chemical radical does not meet either of these tests. The MPEP states in §2162 II.A.(a), that "[p]ossession may also be shown by a clear depiction of the invention in detailed drawings or in ***structural chemical formulas*** (emphasis added) which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention."

10. Claims 38-41, 44, 47, and 49-52 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitations in claims 38-41 "wherein hydroxylation ... the drug moiety" is unduly functional. The limitation in claim 49 is also unduly functional. Which compounds posses these properties? How fast and to what

extent must the reactions occur so that a compound meets these claim limitations? Must the hydroxylation be enzymatic? How is this to be determined and how much experimentation must be employed to determine if a particular compound (or genus of thousands of compounds) are so metabolized?

Applicants made no specific argument regarding this rejection.

11. Claim 52 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants lack enablement for the treatment of cancer generally. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689.

Applicants have amended claim 52 to add a limitation regarding hydroxylase enzymes. Which tumors have this enzyme? Is it possible that all tumor cells possess some detectable level of some enzyme with this ability? Lines 19-20, page 1 contains a list of tumors which contain a "xenobiotic metabolizing enzyme". Is this what is intended? Is CYP1B1 a hydroxylase? If so, the Examiner suggests including the list of tumors to be treated in the claim.

Allowable Subject Matter

12. Claims 43, 45, 46, and 48 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 57 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action.

Conclusion

13. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
August 14, 2002